REMARKS

Claims 1-20 are pending in this application. Claims 1-20 were rejected under the judicially created doctrine of obviousness-type double patenting. Claims 1-20 were rejected under 35 U.S.C. § 112, first paragraph. Claims 1-6 and 9-10 were rejected under 35 U.S.C. § 103.

By this amendment, claim 1 has been amended without prejudice or disclaimer of any previously claimed subject matter. Support for the amendment can be found, *inter alia*, throughout the specification.

The amendments are made solely to promote prosecution without prejudice or disclaimer of any previously claimed subject matter. With respect to all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

The amendment presents the claims in better form for consideration on appeal. Entry of the amendment is respectfully requested.

Applicants have carefully considered the points raised in the Office Action and believe that the Examiner's concerns have been addressed as described herein, thereby placing this case into condition for allowance.

Rejections Under Obviousness-Type Double Patenting

Claims 1-20 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-10 and 12-19 of U.S. Patent Application No. 09/716022, now U.S. Patent No. 6,609,014.

Both the instant application and U.S. Patent No. 6,609,014 claim priority to the same priority documents. U.S. Patent No. 6,609,014 is co-owned by QLT, Inc. and the University of British Columbia. The instant application is solely owned by QLT, Inc.. Thus, the instant application and U.S. Patent No. 6,609,014 are commonly owned by QLT, Inc.

Although Applicants respectfully continue to traverse this ground for rejection for the reasons on record, a terminal disclaimer in view of U.S. Patent No. 6,609,014 has been submitted herewith. Accordingly, withdrawal of this rejection is respectfully requested.

Rejections under 35 U.S.C. §112, first paragraph

Claims 1-20 were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. Applicants respectfully traverse this ground for rejection for the reasons on record.

The Examiner's concern appears to be summarized with the statement that the specification "fails to provide guidance as to how one skilled in the art would go about preventing restenosis or IH or how arteries could be kept from being susceptible to these pathogenic changes ever again." Office Action, page 6. Although Applicants respectfully continue to traverse the Examiner's assessment of the specification for the reasons on record, the term "prevent " has been herein deleted from the amended claim 1 in the interest of expediting prosecution of this application.

In view of the foregoing, Applicants respectfully submit that the enablement requirement has been met and that the rejection under 35 U.S.C. §112, first paragraph may be withdrawn.

Rejection under 35 U.S.C. § 103

Claims 1-6 and 9-10 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Vincent (U.S. Patent 5,422,362) in view of Gonschior *et al.* (*Photochemistry and Photobiology*, 1996: 64(5): 758-763, "Gonschior") and Harrison (*Harrison's Principle of Internal Medicine,* 13th Ed., 1994, page 986). Applicants respectfully traverse this rejection.

The claimed invention is directed to a method in which photosensitizer photodynamic therapy (PDT) is used in adjunct with angioplasty in a human subject to treat, inhibit or reduce restenosis or intimal hyperplasia (IH). The claimed invention is directed to PDT with a particular total energy dose of from about 0.25 to about 25 J/cm^2 to treat, inhibit or reduce restenosis or IH at the treatment site without depleting all endothelial and smooth muscle cells. As described in the specification, damage to the media of a treated blood vessel is a likely event with the use of PDT doses higher than those of the claimed method.[1]

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20USPQ2d 1438 (Fed. Cir. 1991); MPEP §2143. If any one of these three criteria is not met, a *prima facie* case of obviousness has not been established.

[1] See specification, for example, page 9, lines 16-28.

Applicants respectfully submit that cited references do not support a *prima facie* case of obviousness with regard to the claimed invention.

As an initial matter, in the response to the previous Office Action submitted September 8, 2003, Applicants pointed out that the citation of Vincent appeared to be for the descriptions therein of other documents (by Sobeh et al., Dartsch et al., and Eton et al.) rather than for the full teaching of Vincent per se. Applicants then requested clarification as to whether the rejection was based on the full content of each of these other documents per se, rather than the characterization of them reflected in Vincent.

In the present Office Action, the Examiner did not specifically address this request and maintains the rejection in view of Vincent as the primary reference. However, only the descriptions of the other documents (Sobeh et al., Dartsch et al., and Eton et al.) and not the teaching of Vincent in its entirety are discussed in the present rejection. In fact, the Examiner points to a table in Eton et al. that is not referred to in Vincent. Applicants submit that it is still unclear what description on which the Examiner relies for the present rejection and again request clarification regarding this matter.

Applicants herein address the present rejection based on that presented in the Office Action. However, Applicants maintain that there is no motivation to combine or modify the teaching of the primary reference Vincent, a reference that teaches the use of photosensitizers without the use of photoactivation, with a second reference (Gonschior) which uses photosensitizers with photoactivation.

If the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2.d 900, 221 USPQ 125 (Fed. Cir. 1984); M.P.E.P.

§2143.01. Also, a prior art reference must be considered in its entirety, i.e., as a whole, including positions that would lead away from the claimed invention.[2] Thus, although the Examiner points to discussion of references in the background section of Vincent, the entirety of Vincent must be considered and any modification to the teachings of Vincent must not be rendered unsatisfactory for Vincent's intended purpose. Applicants submit that modifying the teaching of Vincent according to the teaching of Gonschior would result in a process which uses photosensitizers with photoactivation, the exact opposite of the teaching of Vincent.

Turning to the allegations in the statement of the rejection, the Examiner states that Vincent "teaches Sobeh using Photofrin II ... to treat restenosis" and that Vincent "teaches Dartsch using Photofrin II to markedly reduce plaque-derived smooth muscle cells without totally destroy the normal viable cells." Office Action, page 10. Applicants again point out that Sobeh et al. and Dartsch et al. as discussed in Vincent[3] are directed to *in vitro* experiments performed on isolated smooth muscle cells in culture and, as such, are different from and are not directed to the claimed subject matter. The treatment of isolated cells in a culture dish is not the same as treating restenosis or IH in a blood vessel in an individual that has undergone angioplasty. Applicants also submit that contrary to the Examiner's assessment of Sobeh et al., Sobeh et al. does not teach restenosis but rather an *in vitro* treatment of human smooth muscle cells with a photosensitizer and photoactivation. Sobeh et al. only discusses the measurement of cell destruction after this treatment and, due to the nature and design of the experiment (e.g., separated cells in a dish), Sobeh et al. cannot and does not address the effect of the treatment on restenosis or IH in a blood vessel in an individual that has undergone angioplasty. Thus, the skilled artisan following Sobeh et al. would have no reasonable expectation of success of such a treatment when administered in an individual after angioplasty. The *in vitro* study by Dartsch et al. measures cell viability after the treatment.

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[2] *W.L. Gore & Associates, Inc. v. Garlock, Inc.*. 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984).

[3] See Vincent column 2, lines 12-57.

Again, the comparison of the treatment of isolated cells in culture and the treatment of cells in the blood vessel environment would not provide a reasonable expectation of success for the claimed method.

In response to this argument when previously presented, the Examiner states the following at page 12 of the Office Action:

> "Although treatment of cell cultures as not the same as treating restenosis or IH in a blood vessel that undergoes angioplasty, this is not the standard of obviousness rejection. It is common practice in the pharmaceutical field to use non-human model to serve as a predictor of whether the agent will be successful or not in clinical trials. Therefore, the reasonable expectation of success is present in non-human study that shows therapeutic efficacy."

Applicants agree that a non-human animal model that demonstrates therapeutic efficacy can serve to predict success in a clinical trial. However, Sobeh et al. and Dartsch et al. describe *in vitro* experiments in which the cells of interest are removed from their blood vessel environment, dissociated from their neighboring cells, and treated in a culture dish. These references do not demonstrate treatment in adjunct with angioplasty. The measured response to this treatment is cell destruction or loss of cell viability. Sobeh et al. and Dartsch et al. do not show an effect on restenosis or IH, processes that take place in, and in response to, the complex environment of a blood vessel. Further, Sobeh et al. and Dartsch et al. do not show an effect on restenosis or IH in a blood vessel in response to angioplasty. Thus, the teaching of these references is not the same as the claimed method. The basis of the distinction between the claimed invention and Sobeh et al. and Dartsch et al. is not human vs. non-human but rather an *in vitro* experiment vs. a PDT treatment in a blood vessel of an individual after angioplasty.

These references, alone or in combined with the others, would not provide a skilled artisan a reasonable expectation of success for the claimed method. Thus, these references do not support a *prima facie* case of obviousness.

The Examiner states that Vincent "teaches Eton et al. reported that Photofrin II and irradiation significantly improve the ratios of the area of IH to that enclosed by the internal elastic lamina." The description of Eton et al. in Vincent however, is silent with regard to the time and intensity of the radiation to accomplish a reduction of IH, thus this description does not teach PDT with the low total energy doses as claimed. Also, neither the description of Eton in Vincent, nor the reference of Eton et al. *per se*, describe the use of PDT in adjunct to angioplasty.

Gonschior describes the use of photofrin with 100 J of light energy (see page 759, left column) in the PDT treatment of injured tissue but does not teach or suggest the low total energy doses as claimed. Gonschior also does not perform the PDT procedure in adjunct to angioplasty. The PDT treatment in Gonschior was performed immediately after the blood vessel was damaged. Thus, contrary to the claimed invention in which PDT treatment is used in adjunct with angioplasty, Gonschior does not describe PDT treatment of blood vessels afflicted by pre-existing disease. In fact, Gonschior notes this limitation of their study and warns against extrapolation of the results with the following from page 761, right column:

> "[t]he use of injury to nondiseased arteries in young pigs is a limitation of the study and we can only therefore conclude that PDT reduced certain aspects of the pathophysiology of restenosis. Thus, perhaps the results cannot be directly extrapolated to use in human restenosis where the process occurs in human atherosclerotic vessels...." .

As noted above, a cited reference must be considered in its entirety, i.e., as a whole, thus, one is not permitted to ignore the above statements of Gonschior which point out limitations of the

study. Applicants respectfully submit that neither Vincent (Eton et al.) or Gonschior, alone or combined, provide an expectation of success in the practice of the invention as claimed.

At best, it appears that this rejection in view of these references is based on an improper "obvious to try" standard. As noted in *In re O'Farrell* (853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988)), an "obvious to try" situation exists "when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued."[4] This describes the instant situation exactly in that the teachings of Eton et al. or Gonschior may pique the curiosity of the ordinary artisan to investigate whether PDT will work against IH in adjunct with angioplasty. But that ordinary artisan has no expectation that success would result.

Harrison provides a general description of percutaneous transluminal coronary angioplasty. Harrison notes that occurrence of restenosis "appears to result from excessive fibrotintimal proliferation and local smooth -muscle cell hyperplasia" and that "no mechanical or pharmacologic strategy has substantially reduced this restenosis rate."[5] Harrison is silent with regard to the use of PDT and PDT in adjunct with angioplasty. Thus, Harrison provides no disclosure to rectify the deficiencies of Eton et al. or Gonschior.

In sum, Applicants respectfully submit that there is no motivation to combine or modify the teachings of the cited references to arrive at the claimed invention. Further, references, either alone or combined, provide no expectation of success for the claimed invention as discussed. Still further, the cited references, either alone or in combined, do not teach or suggest all of the claim

[4] See *In re Eli Lilly & Co.*, 902 F.2d 943, 14 USPQ2d 1741 (Fed Cir. 1990).
[5] See, Harrison, page 986, right column.

limitations. None of the cited references describe the use of PDT with the particular claimed total energy doses in adjunct to angioplasty.

Accordingly, the cited references do not support *prima facie* obviousness with regard to the claimed invention.

Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §103.

CONCLUSION

Applicants believe that all issues raised in the Office Action have been properly addressed in this response. Accordingly, reconsideration and allowance of the pending claims is respectfully requested. If the Examiner feels that a telephone interview would serve to facilitate resolution of any outstanding issues, the Examiner is encouraged to contact Applicants' representative at the telephone number below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 273012012200.

Dated: May 3, 2004

Respectfully submitted,

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